5. (Three times amended) A composition of matter comprising a plurality of a thousand or more different polynucleotides selected from cDNA molecules or fragments of a target polynucleotide, said composition including a mixture of microparticles,

wherein each microparticle has polynucleotides of the plurality attached thereto,

and wherein substantially all different polynucleotides in the plurality are attached to different microparticles.

Also enclosed, starting on a separate page following this response, is a marked copy of the presently amended claim showing all changes relative to the previous version.

REMARKS

Reconsideration of the rejections set forth in the Office action mailed April 10, 2001 is respectfully requested. Claims 1-6 and 8-13 are currently under examination.

I. Amendments

Independent claim 5 has been amended to specify that the plurality of polynucleotides includes at least a thousand members. Support is found in the specification at, for example, column 3, lines 2-5; column 14, lines 38-39; and column 21, lines 56-58.

The sequence listing has been revised to correct formal errors, as set out in the "Raw Sequence Listing Error Report" enclosed with the Office Action, and to rectify substantive problems pointed out by the Examiner, as discussed further below.

No new matter is added by any of the amendments.

II. Original Patent

The original ribbon copy of U.S. Patent No. 5,654,413 is enclosed herewith.

III. Sequence Listing

The following sequences, employing the numbering introduced in the amendment filed on 2/10/01, have been corrected to reflect the sequence information in the specification.

The applicant notes that these corrected sequences are identical to SEQ ID NOs: 1, 2, 4, 11, 12, 13, and 14, respectively, of recently issued U.S. Patent No. 6,280,935, which was also examined by Examiner Shibuya. Accordingly, they should be found acceptable by the Examiner in the present

application.

SEQ ID NO: 5 has been corrected to:

CTAGTCGACC ANNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNTTT TTTTTTTTTT TTTTTT

to reflect the description at col 15, lines 5-13 of the specification (where "[W,W,W,C]" represents a four-nucleotide subunit with one C and three W's (A or T) in any order, as shown, for example, in Table II, column 7).

SEQ ID NO: 4 has been corrected to:

NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNTGG

to reflect the description at col 15, lines 17-21of the specification.

SEQ ID NO: 19 has been corrected to:

RCGACCANNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNTTTTTTT TTTTTTTTTT TT

to reflect the description at col 15, lines 36-40 of the specification.

SEQ ID NO: 9 has been corrected to:

TCGACCGATT TGATTAGATT TGGTAAAGTA ATGTAAAGGA TTA;

SEQ ID NO: 10 has been corrected to:

TCGACCAGTA ATGTAAAGGA TTTGATAGTA TTTGTGATGA TTA; and

SEQ ID NO: 17 has been corrected to:

TCGACCTAGA TGATGATTGA TTGTAAAAAG AAAGTTTGTT TGA

to reflect the description at col 24, lines 1-17 of the specification, where the "(w_i)" subunits have the meanings given in Table I, column 7.

SEQ ID NO: 18 has been corrected to:

GGGCCNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NA

to reflect the description at col 25, lines 24-28 of the specification.

The applicant submits that the specification and sequence listing are now in accordance with the requirements of 37 CFR §1.821 through 1.825.

III. IDS

The Examiner requested an indication as to which prior applications would contain the references cited on the form PTO-1449 which was faxed on 5/17/01.

As noted on the faxed form PTO-1449 (though not in the most apparent location), references marked with one star on the form were submitted in parent application no. 08/322,348, and references marked with two stars were submitted in parent application no. 08/358,810.

A Supplemental IDS containing the cited references will be submitted shortly under separate cover.

IV. Allowable Subject Matter

Claims 1-4 and 9-13 were found allowable over the prior art.

V. Rejections under 35 U.S.C. §102(b)

Independent claim 5 was rejected under 35 U.S.C. §102(b) as being anticipated by Wang, EP 304845 A2. This rejection is respectfully traversed for the following reasons.

The standard for lack of novelty, that is, for anticipation, is one of strict identity. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d 1367, 231 USPQ 81, 90 (Fed. Cir. 1986); *In re Donohue*, 766 F2d 531, 226 USPQ 619, 621 (Fed. Cir. 1985). To anticipate a claim for a patent, a single prior source must contain all its essential elements.

A. The Invention

The applicant's invention, as embodied in claim 5, comprises:

a composition of matter comprising a plurality of a thousand or more different polynucleotides, selected from cDNA molecules or fragments of a target polynucleotide, said composition including a mixture of microparticles,

wherein each microparticle has polynucleotides of the plurality attached thereto,

and wherein substantially all different polynucleotides in the plurality are attached to different microparticles (i.e., each microparticle has only one kind of polynucleotide; see col 14, lines 18-19).

B. The Prior Art

Wang describes "labelled microbeads to which gene probe molecules are linked", for use in determining the presence and/or quantity of target sequences in mRNA. The disclosure also teaches that microbeads may be differently labeled with different trace elements (e.g. Cr, Fe, Zn, and Ba; see page 4, line 52), and that differently labeled beads may contain different probes, so that different

assays, e.g. for expression of different oncogenes, may be carried out simultaneously. See e.g. page 4, line 53 to page 5, line5.

There is no indication in the reference, however, that the number of different polynucleotides used as "gene probes" would number a thousand or more. In the Example on page 7, which describes simultaneous assay for expression of *ras* and *myc* oncogenes, the *ras* and *myc* probes are formed "through binding of a poly(G)-extended oncogene probe sequence" to a poly(C)-containing microbead. The formation is further described on page 8 as follows: "A poly(dC)-coated microbead reporter labelled with Ti and a poly(G) extended anti-sense probe for *myc* are mixed....Another poly(dC)-coated microbead reporter, labeled with Cr, and a probe for *ras* are prepared in the [same] way." The probes are then contacted with an mRNA sample for the assay.

In this example, two different polynucleotides are attached to microbeads. While the reference teaches the use of "several" differently labeled microparticles bearing different probes (page 4, lines 47-48) (and one could even conceive that multiple sequences could be used for probing expression of an oncogene, rather than just one), there is clearly no disclosure of "a thousand or more" different sequences in a microbead population, where "substantially all different polynucleotides in the plurality are attached to different microparticles."

Since the reference does not disclose all of the elements set out above in claim 5, the claim cannot be anticipated by this reference under 35 U.S.C. §102(b). In view of this, the applicant respectfully requests the Examiner to withdraw the rejection under 35 U.S.C. §102(b).

VI. Rejections under 35 U.S.C. §103

Claims 5, 6, and 8 were rejected under 35 U.S.C. §103 as being unpatentable over Wang, above, in view of Hornes *et al.*, U.S. Patent No. 5,512,439. These rejections are respectfully traversed in light of the following remarks.

A. The Invention

The applicant's invention, as embodied in independent claim 5, comprises, as noted above: a composition of matter comprising a plurality of a thousand or more different polynucleotides, selected from cDNA molecules or fragments of a target polynucleotide, said composition including a mixture of microparticles; wherein each microparticle has polynucleotides of the plurality attached thereto; and wherein substantially all different polynucleotides in the plurality are attached to different microparticles (i.e., each microparticle has only a single kind of polynucleotide; see col 14, lines 18-19).

Dependent claim 6 provides that each microparticle bears about 10^5 polynucleotide molecules.

Dependent claim 8 provides that the plurality of polynucleotides includes from ten (thousand) to a hundred thousand different members.

B. The Cited Art

Wang is discussed above. As noted above, the reference does not teach "a thousand or more" different sequences in a microparticle population, where "substantially all different polynucleotides in the plurality are attached to different microparticles."

Hornes *et al.* is directed to the advantages provided by the use of monodisperse superparamagnetic particles in applications in which molecules such as oligonucleotides are attached to magnetic particles, as set forth in the Background of the Invention.

Hornes does teach that "each magnetic particle carries 10^3-10^5 probes", at column 5, lines 12-14, as noted by the Examiner. However, there is no teaching in Hornes of a microparticle population where "substantially all different polynucleotides" in a plurality of a thousand or more different polynucleotides "are attached to different microparticles", as claimed. At columns 5-11 of the Hornes patent, several uses of the magnetic particles are described, and kits directed to these uses are described at column 12. As can be seen from these descriptions, each of these applications employs a magnetic particle population bearing a single polynucleotide: i.e., oligo-dT; a "specific oligonucleotide"; or a "standard specific DNA probe/primer for the 3' end of the target nucleic acid" (column 12, lines 1-2, 7-8, 13-14, and 23-25).

C. Analysis

In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references or in knowledge generally available to one skilled in the art, to modify a reference or combine reference teachings. The prior art must also provide a reasonable expectation of success. Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. (MPEP §2143)

Neither Wang nor Hornes teaches or suggests a composition including a plurality of a thousand or more different polynucleotides, and a mixture of microparticles, wherein each microparticle has polynucleotides of the plurality attached thereto, and wherein substantially all different polynucleotides in the plurality are attached to different microparticles. The disclosed populations of microparticles in these references contain anywhere from one to "several" different sequences, and there is no suggestion to prepare a microparticle population containing a thousand or more different sequences.

Nor is there any suggestion in either reference of how one would go about preparing such a composition. The methods described in Hornes for attaching polynucleotides to the particles (column 4) involve routine reaction of a functional group on the particle with a functional group on a polynucleotide, and would not provide for attaching substantially all different polynucleotides of a large population to different microparticles. In Wang, the particles bearing different probes are prepared in separate syntheses (page 8), a method that would clearly be ineffective for a thousand or more such probes.

In view of the above, the applicant respectfully requests the Examiner to withdraw the rejections under 35 U.S.C. §103.

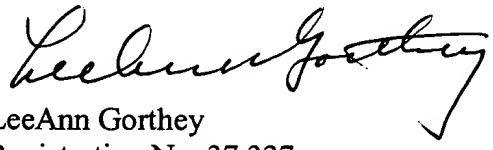
VII. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4403.

No further fees are believed necessary with this communication. However, the Commissioner is hereby authorized and requested to charge any deficiency in fees herein, or credit any overpayment, to Deposit Account No. 50-0665.

Respectfully submitted,



LeeAnn Gorthey
Registration No. 37,337

Date: 12-9-01

Correspondence Address:
PAYOR NUMBER 22918
PHONE: (650) 838-4403
FAX: (650) 838-4350

5. (Three times amended) A composition of matter comprising a plurality of a thousand or more different polynucleotides selected from cDNA molecules or fragments of a target polynucleotide, said composition including a mixture of microparticles,

wherein each microparticle has polynucleotides of the plurality attached thereto,

and wherein substantially all different polynucleotides in the plurality are attached to different microparticles.